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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/669,768
Filing Date: September 24, 2003
Appellant(s): SHEN ET AL.

Gary Fabian
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 12/12/08 appealing from the Office action mailed 1/15/2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Kirn, D, "Replication -selective oncolytic adenoviruses: virotherapy aimed at genetic targets in cancer" Oncogene, vol19 (2000), pp6660-6669.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 11, 12, 24, 28, 33, 39 and 40 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of cancer characterized by p53 loss or deficiency by direct administration Onyx 051 and 053 (comprises a single amino acid substitution in amino acid 240 or 260), does not reasonably provide enablement for any other embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat.

App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention**. The instant invention is drawn to recombinant adenovirus comprising single amino acid mutations in the E1B-55K gene such that binding to p53 is reduced as compared to binding between p53 and wild-type E1B-55K. The invention utilizes disciplines of molecular biology, virology and clinical technology.

2) **Scope of the invention**. Applicants' claims are broadly drawn to treatment using recombinant adenovirus *comprising any single amino acid mutation* in E1B-55K such that binding to p53 is reduced. Applicants' disclosure teaches development of two such mutants in which amino acid 240 and 260 are mutated to generate Onyx 051 and Onyx 053. These mutants are not able to bind to p53. As described in the specification, the method of the instant invention is directed toward treating cancer using the vectors and is based upon oncolytic replication function of the viruses in infected tumor cells.

3) **Number of working examples and guidance**. The instant invention is drawn to single amino acid mutations within E1B-55k that affect binding to p53. Applicants have constructed 26 mutant rAd in which a single amino acid within the E1B-55K coding sequence was mutated (see e.g. page 12, ¶ 4 and table 2). Two of these mutant R240A and H260A lost ability to bind p53 but did not lose late viral function. Furthermore, the cells were tested for oncolytic affect. U20S and Du145 cells were assayed and demonstrated that the two viruses were cytotoxic.

4) **State of Art**. Enormous efforts have been directed toward the development of vectors for cancer treatments. Adenovirus mutants that lack the ability to bind to p53 are replication

deficient in non-replicating, non-neoplastic cells with p53 but in cells deficient in p53, the virus is replicative and oncolytic. Previously, the art has described generation of rAd comprising deletions, substitutions and frame-shifts which inactivate the ability of E1B-55K to bind to p53 efficiently to generate E1B-p53- mutants. For example, ad2 dl1520 (Onyx 015) comprises a frame-shift mutation at nucleotide position 2022 that generates a stop codon 3 amino acids downstream of the AUG codon resulting in deletion of large region of E1B, US patent 5,677,178 describes the generation of rAd lacking E4orf6 and US 6,080,578 teaches construction of Onyx 019, 020 and 021 in which various amounts of internal sequences are deleted. Kirn et al teach that "the role of p53 in replication-selectivity of dl1520 has been difficult to confirm despite extensive *in vitro* experimentation by many groups, E1B-55K gene deletion was associated with decreased replication and cytopathogenicity in p53(+) tumor cells versus matched p53(-) tumor cells, relative to wild-type in RKO and H1299 cells" (page 6653, col 1, ¶ 3). Therefore, the efficacy of the instant adenovirus lies in treatment of p53 (-) tumors. This efficacy has been specifically observed when in combination with chemotherapy (see Kirn et al, page 6666, col 1).

5) **Unpredictability of the art**. The instant invention is unpredictable for treatment of cancer in humans given the broad recitation of a genus of adenovirus for delivery to p53 lacking neoplastic cells wherein the adenovirus have reduced binding to p53. The instant invention is based upon the premise that targeted mutations within E1B-55K result in a virus that is replicative in tumor cells lack p53 while normal cells do not. As well the specification teaches that this premise is distinctly connected to the replicative condition of the rAd. However, by recitation that the rAd comprises a single amino acid mutation in E1B-55K, the adenovirus to be used in the treatment encompasses a broad and diverse genus of adenoviruses that need only be

linked by a mutation in E1B-55K. Rather the nature of the adenoviruses for treatment of cancer according to the instant invention must be replicative. To this end, applicants generated 26 mutants but only two of these mutants are capable of reduced binding to p53. These mutants (Onyx 051 and 053) comprise a single mutation in amino acid 240 and 260.

Hence, applicants have elucidated the unpredictability of any single amino acid to produce the required functional requirements as only two mutants of 26 produced have the recited functional requirements. As well, applicants have not provided the structural requirements of the single amino acid mutants such that one of skill in the art would be able to identify those mutants that have lost the ability to bind efficiently to p53. Hence, the unpredictability of using the claimed invention in gene therapy is accentuated due to the broad and unpredictable nature of the identifying adenovirus with single amino acid mutations in the E1B 55k gene that have lost the ability to bind p53 and furthermore be used to treat cancer.

6) **Summary**. In view of predictability of the art to which the invention pertains: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

(10) Response to Argument

Applicants' arguments filed on pages 10-27 of the Appeals Brief filed 12/12/08 have been fully considered but they are not persuasive. Applicants argue that the specification

provides enablement commensurate in scope with the claim invention coupled with the available knowledge about that E1B techniques to produce mutants. However, the instant claims are directed to treatment of cancer and herein lies the unpredictable nature of the claim. The instant invention requires use of an adenovirus to treat neoplastic cancer lacking p53 wherein the adenovirus is oncolytic and has reduced binding ability to p53 wherein the adenovirus comprises a single amino acid mutation in E1B. To this end, the instant invention is only enabled for treatment of cancer by administration of Onyx 051 and Onyx 053. These are two viruses that have single amino acid mutations in E1B and wherein the viruses have reduced binding to p53 and retain late viral function in the cell. These two mutants are recited in dependent claims 13, 25-27 and 35-38, currently objected to as dependent on a rejected claim. Treatment protocols as established in the specification require these functions for selective oncolysis. Given the large breadth of the claims in light of the unpredictable nature of cancer treatments and the unpredictable nature of developing oncolytic virus, the invention requires undue experimentation.

The invention is based upon the art of cancer therapy utilizing adenovirus to selectively lyse cancer cells (see specification page 1, line 13-15). As set forth in the specification, oncolytic treatments initially used wild-type viruses. As, there was no significant alteration in the course of disease with wild-type virus, selectively replicative viruses active in neoplastic cells were devised for example, as found in this case, dependent upon p53 status of the cell. Onyx 015 was the gold standard for many years of such virus. This virus is a mutant adenovirus that does not express the E1B-55K protein as it comprises a stop codon immediately following the translation initiation codon ATG, plus a large deletion of the E1B-55K coding sequence.

However, the success of Onyx-015 was found to be limited, attributable to loss of viral late function, which is absolutely necessary for viral replication. As set forth in the specification, page 3, line 14-21, "While the lack of E IB-55K function in ONYX-015 permits viral replication in tumor cells that lack p53 function, the virus is also defective in cytoplasmic accumulation of the viral late mRNAs, host cell shut-off, and translation of late mRNAs. Thus, the mutation in ONYX-015 compromises the ability of the mutant virus to reproduce itself in tumor cells. As such, it would be highly desirable to create an E1B-55K mutant that fails to bind and inactivate p53, yet is still capable of performing the late viral functions." Hence, applicants and the art have set out to establish treatment protocols using adenovirus that *can* replicate in cells and have reduced binding to p53 to improve upon this lack of function in Onyx-015 and to provide treatment protocols with distinct requirements from that of Onyx-015. To this end, applicants propose mutant adenovirus comprising a single amino acid mutation in the E1B 55 K region so that the virus replicates in neoplastic cells without affecting surrounding or healthy cells. Furthermore, applicants only demonstrate two mutants This delicate balance is an absolute requirement for efficacy and safety of treatment.

The specification teaches the difficult nature of achieving such precise goals. In part, mutating the small region of E1B responsible for p53 binding and for late function such that cancer can be treated successfully was highly unpredictable. "A basis of the present invention is that the regions of the E1B-55K protein that mediate these functions appear to overlap with one another. The region of E IB-55K that mediates its interaction with p53 has been mapped to amino acid 224 to 354 (Kao, C C. et al., Virology, 1990, vol. 179: p. 806-814; and, Yew, P. R., et al., Virology, 1990, vol. 179: p. 795-805). The same region appears to be critical for EIB-

55K's ability to mediate mRNA transport. The regions required for E4orf6 binding (Rubenwolf, S.et al., J. Virol., 1997, vol. 71 : p. 1 I 15-1123), the regions required to bind E 1B-AP5, a cellular protein implicated in nucleocytoplasmic transport (Gabler, S., et al., J. Virol., 1998, vol. 72: p. 7960-7971), and the regions of EIB-55K that have RNA binding capability (Horridge, J. J. and K. N. Leppard, J. Virol., 1998, vol. 72: p. 9374-9379) all partially overlap with the region required for p53 binding. Thus far, all efforts to separate the p53 binding/inactivation and the late functions of the protein have been unsuccessful (ibid bridging ¶ page 10-11, emphasis added)." Figure 1 depicts 26 mutants tested wherein only 2 had potential to use in treatment protocols. "More specifically, we have constructed twenty-six single amino acid substitution mutations in the p53-binding domain and the transcriptional repression domain of the E1B-55K protein. These mutations were recombined into an infectious virus, d1309, (see, Jones, N and T. Shenk, Cell, 1979, vol.17: p. 683- 689) background and characterized for their abilities to modulate p53 level and activity, interact with the E4orf6 protein, mediate viral late gene expression and host cell shut-off, rescue the cold sensitive phenotype, and support virus replication in human cancer cells. Two E 1B-55K mutants, R240A and H260A, appeared to have lost the ability to inactivate p53 but have retained, at least partially, the late functions of the wild-type protein. R240A fully restored the wild-type replication capacity of ONYX-015 in human cancer cells, while H260A did so partially. The ability to separate the p53-inactivation activity and the late functions of El B-55K raises the possibility of creating adenovirus variants that replicate more efficiently than ONYX-015 but retain the tumor selectivity of ONYX-015" (ibid, page 12, line 10-20). Hence, contrary to applicants' arguments, the screen provided in the specification can not be considered

to be a proper screen for cancer treatment wherein the treatment requires oncolysis by a virus without or with reduced p53 binding.

The MPEP teaches, "However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). (see MPEP 2164.08(b). In the instant case, the invention is directed to cancer treatment using oncolytic virus. To this end, applicants propose mutant adenovirus comprising a single amino acid mutation in the E1B 55 K region so that the virus replicates in neoplastic cells without affecting surrounding or healthy cells. Hence, while the specification teaches a single amino acid in the E1B 55K protein and assess function of singly mutated adenovirus, the claims encompass a number of mutations. In light of the expressed difficulty in achieving the stated goals, the number of ineffective virus and that the state of the art of such therapy has been established to be highly unpredictable, it would require undue to develop virus with selective oncolysis wherein the virus have reduced p53 binding allowing replication to proceed in neoplastic cells and still maintain replication function.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Maria Marvich

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